REMARKS

Claims 11, 2, 3, 20, 21, 22, 39, 40, and 41 have been amended. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, 50, and 58-73 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 under 35 U.S.C. § 112, Second Paragraph

Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the following grounds.

Ground 1: The Office Action states that claims 1 and 20 are allegedly vague and indefinite due to the phrase "A method of producing a heterologous biological substance... .wherein the mutant cell comprises a first nucleic acid sequence encoding a heterologous protein, wherein the heterologous protein is the heterologous biological substance *or the heterologous protein is involved in the synthesis* of *the heterologous biological substance"* because the method recited in steps (a) and (b) appears to be a method of recombinant protein production, yet the new limitation does not convey this fact. The Office Action also states that the way the claim has been amended, *e.g., or the heterologous protein is involved in the synthesis* of *the heterologous biological substance,* does not convey that the method is completed at step (b).

Claims 1 and 20 have been amended to recite a "heterologous protein".

Ground 2: The Office Action states that claim 20 is vague and confusing due to the phrase "comprising a modification of at least one of the genes *cypX* and *yvmC* " because the mere recitation of a name, *i.e., cypX* and *yvmC,* to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept and the claim should provide any structural properties, *e.g., cypX* comprising the nucleotide sequence set forth in SEQ ID NO: 1 and *yvmC* comprising the nucleotides sequence of SEQ ID NO: 7, to adequately define the genes.

Applicants have amended claim 20 to recite "wherein the *cypX* gene comprises the nucleic acid sequence of SEQ ID NO: 1 or comprises a nucleic acid sequence having at least 70% homology to SEQ ID NO: 1, and the *yvmC* gene comprises the nucleic acid sequence of

SEQ ID NO: 7 or comprises a nucleic acid sequence having at least 70% homology to SEQ ID NO: 7".

Ground 3: The Office Action states that claim 20 is vague and indefinite due to the term "heterologous biological substance" because it is unclear what substance other than a protein could be made from the claimed transformed host.

Claim 20 has been amended to recite a "heterologous protein".

Ground 4: The Office Action states that in claim 20 "modification" should be changed to "mutation" and specifically recite that the mutation results in loss of red pigment production because the claim does not directly correlate the mutation to the loss of pigment.

Applicants respectfully point that claim 20 was amended in the Amendment of November 30, 2005 in accordance with the Office's suggestions above.

Ground 5: The Office Action states that claim 39 is vague and indefinite due to the term "heterologous biological substance" because it is unclear what substance other than a protein could be made from the claimed transformed host.

Claim 39 has been amended to recite a "heterologous protein".

Ground 6: The Office Action states that claim 39 is incomplete for omitting essential steps because the mutant of a parent of Bacillus cell has not been 'obtained' as required in the preamble and the method ends with the identification of the mutant cell, not the obtaining or isolation of said cell.

Claim 39 has been amended to recite "isolating the mutant cell from step (a) comprising the mutation of at least one of the genes *cypX* and *yvmC*".

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 under 35 U.S.C. § 112, First Paragraph

Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office Action stated:

> The instant specification has taught that the *cypX* gene set forth in SEQ ID NO: 1 and the *yvmC* gene set forth in SEQ ID NO: 7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-

> purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO: 1 and the *yvmC* gene set forth in SEQ ID NO: 7 from *Bacillus subtilis.* It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID NOs: 1 and 7. The specification is only enabled for methods which use *B. subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO: 7 and not the broad scope of the claims. It would take one of skill in the art undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus.* Bacterial species often times do not produce the same proteins. The prior art is silent as to whether any other species of *Bacillus* possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B. subtilis.*

This rejection is respectfully traversed for the reasons of record and further for the reasons below.

Applicants submit that the specification complies with the enablement requirement.

It is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed ..." *Ex parte Jackson*, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

As stated in the record, the reasoning provided by the Office Action is that the specification is enabled only for methods which use *Bacillus subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and it would require undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus*. We respectfully disagree with this assertion for the reasons of record. Applicants have shown in Example 6 that primers based on the *cypX* gene from *Bacillus subtilis* were used to clone by PCR the *cypX* gene from *Bacillus licheniformis* and delete a portion of the gene to prevent formation of the red pigment. Consequently, one of ordinary skill in the art can

use the *cypX* and *yvmC* genes isolated from *Bacillus subtilis* (see Examples 1 and 2) to synthesize primers based on either the *cypX* gene or *yvmC* gene from *Bacillus subtilis* to clone by PCR the corresponding genes from other *Bacillus species* and delete a portion of such genes to prevent formation of the red pigment.

Furthermore, the specification contains an extensive disclosure of techniques which are well known in the art and indeed routine for persons of ordinary skill in the art for identifying and using other *cypX* and *yvmC* genes as described in the record. It is well within the skill of the art to discover new red pigment genes in other species of *Bacillus* using Applicants' disclosure, as exemplified in Example 6 of the specification for *Bacillus licheniformis*. Applicants clearly demonstrate that it it would NOT require undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus*.

The Office asserts that tossing out the mere germ of an idea does not constitute enabling disclosure and that while every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. The Office's assertion is without foundation based on the discussion above. *Bacillus* hosts with the desirable traits of increased protein expression and secretion may not necessarily have the most desirable characteristics for successful fermentation, recovery, and purification of biological substances produced by the cells because of pigment formation requiring removal during the recovery and purification of the biological substance of interest or the pigment may co-purify with the biological substance. Applicants have clearly provided to the art a solution to this problem.

Applicants submit, thereofre, that the claimed inventions are enabled by the specification based on the specification's extensive disclosure of techniques which are well known in the art and indeed routine for persons of ordinary skill for making and using the claimed subject matter of the present invention. Based on Applicants' disclosure, it would be routine for one of ordinary skill in the art to make and use the claimed nucleic acid sequences.

The question, then, is whether in an unpredictable art, Section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with a multitude of red pigment genes. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to

discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous red pigment gene.

If one skilled in this art wished to identify and isolate a red pigment gene other than the one disclosed in Applicants' specification, he would merely read Applicants' specification for directions how to make and use another red pigment gene. Applicants' claimed invention is not complicated, and no special equipment or unusual procedures must be provided when practicing the invention. The methods for cloning another red pigment gene and determining its relatedness to the disclosed red pigment genes is well described in Applicant's specification and well known in the art. One skilled in the art would then merely have to substitute the other red pigment gene. Thus, there is no basis for concluding that persons skilled in this art, armed with the specification, would have to exercise undue experimentation to determine which red pigment genes to use in Applicants' claimed invention and which ones not to use. While some experimentation is necessary to identify other red pigment genes, such experimentation is a simple process and well known in the art. The experimentation would not be undue and certainly would not require ingenuity beyond that expected of one of ordinary skill in the art.

Applicants assert, therefore, that the specification complies with the enablement requirement and respectfully requests reconsideration and withdrawal of the rejection.

For the foregoing reasons, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 under 35 U.S.C. § 112, First Paragraph

Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47, and 50 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> The specification only teaches the *cypX* gene set forth in SEQ ID NO: 1 and the *yvmC* gene set forth in SEQ ID NO: 7 from *Bacillus subtilis.* It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification onyl provides adequate written description for methods which use *B. subtilis* genes and

mutations of the *cypX* aene set forth in SEQ ID NO: 1 and the *yvmC* gene set forth in SEQ ID NO: 7 and not the broad scooe of the claims.

This rejection is respectfully traversed for the reasons of record and further for the reasons below.

Applicants submit that the specification complies with the written description requirement.

The present invention is directed to method of producing a heterologous protein, comprising: (a) cultivating a mutant of a parent *Bacillus* cell in a medium suitable for the production of the heterologous protein, wherein the mutant cell comprises a first nucleic acid sequence encoding the heterologous protein and a second nucleic acid sequence comprising a mutation of at least one of the genes *cypX* and *yvmC*, wherein the mutation renders the mutant cell deficient in the production of a red pigment compared to the parent *Bacillus* cell when cultivated under the same conditions, wherein the *cypX* gene comprises the nucleic acid sequence of SEQ ID NO: 1 or comprises a nucleic acid sequence having at least 70% homology to SEQ ID NO: 1, and the *yvmC* gene comprises the nucleic acid sequence of SEQ ID NO: 7 or comprises a nucleic acid sequence having at least 70% homology to SEQ ID NO: 7; and (b) recovering the heterologous protein from the cultivation medium.

It is well settled that "[t]he test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter ..." *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). In fact, "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly and Co.*, 43 U.S.P.Q.2d at 1569. The test is not whether one of ordinary skill in the art envisions all of the claimed subject matter, as suggested in the Office Action.

The Federal Circuit provides that the written description requirement for a genus of DNAs

is met by a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus or by a recitation of structural features common to the members of the genus.

It is well established in the art that the definition of a genus of genes is accomplished by using structural features that show the relatedness of the genes and their encoded products. For decades the scientific community has employed three structural features to define the relatedness of genes and their products. The three structural features are (1) percent identity of the amino acid sequences encoded by the genes, (2) percent homology of the nucleic acid sequences of the genes, and (3) nucleic acid hybridizations under defined stringent conditions to identify complementary strands of genes encoding the same or similar enzyme or protein function. These structural features have been used to predict the function of polypeptides encoded by novel genes, and to place them in an existing genus.

In the claims at issue, Applicants provide a recitation of one of these structural features common to the claimed genera: (1) a nucleic acid sequence having at least 70% homology to SEQ ID NO: 1, and (2) a nucleic acid sequence having at least 70% homology to SEQ ID NO: 7.

Limiting the literal scope of protection of such a new genus or family to the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 7 provides little incentive to an Applicant to seek patent protection because biological diversity dictates that there will be natural variation in the sequences of other homologous genes existing in nature that are structurally- and functionally-related. Biological diversity in a given gene sequence can easily be found. As genes that fulfill a similar function in different species have evolved from a common ancestor, natural variation in the nucleic acid sequence will rapidly evolve following this speciation. Sequence variation within a single species is also common. Alternatively, the skilled artisan could easily circumvent the literal scope of protection by preparing a variant containing an insertion or deletion of one or more amino acid residues and/or the substitution of one or more amino acid residues by different amino acid residues.

The Office implies that the specification does not adequately describe those structural, physical and chemical characteristics of the claimed nucleic acid sequences having at least 70% homology to SEQ ID NO: 1, and the nucleic acid sequences having at least 70% homology to SEQ ID NO: 7. As mentioned above, the structural feature of percent homology at the DNA level has been used for decades by persons of ordinary skill in the art to determine the relatedness of genes with respect to structure and function of their encoded products to

ascertain whether they belong to the same genus or family. The scientific literature abounds with disclosures of this structural feature to describe the relatedness of genes and their encoded products as well as to distinguish a protein and its gene from other proteins and their genes.

It is well established in the art that there is a definitive relationship between function and % homology at the nucleotide level. Percent homology is highly predictive of function and without this tool it would be impossible to make meaningful annotations of genomes in sequencing projects. Genes that share 70% homology are known to encode products that possess the same catalytic/biochemical function which has formed the basis for genome annotation and comparative genomics. In fact, 70% homology is an extremely conservative criterion for judging functional similarity. A long history of structure-function studies has demonstrated that single domain proteins that share substantial similarity (and >30% homology) over their entire length (>80 residues) without introduction of numerous gaps are almost certainly homologous (derive from a common evolutionary ancestor) and share the same three-dimensional structure (see Martı´-Renom MA, Stuart AC, Fiser A, Sanchez R, Melo F, Sali A. Comparative protein structure modeling of genes and genomes. *Annu Rev Biophys Biomol Struct* 2000; 29:291–325). At the 70% level of homology, the encoded products of genes in related species are virtually guaranteed to share the same catalytic function and substrate specificity. A simple search of any public database using the criteria above for a reference gene of interest will prove that there is a definitive relationship between function and % homology at either the nucleotide or amino acid level.

In fact, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001).

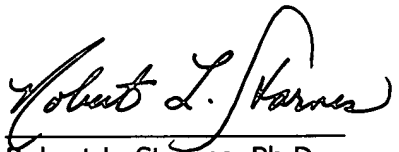
In the claims at issue, the claimed structural feature of percent homology specifies a family of structurally- and functionally-related genes. Since the claimed structural features provide a correlation between function and structure, the written description requirement is satisfied.

For the foregoing reasons, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



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